relative shifts and positional correction of said bondings take place automatically] said step of aligning is automatic.

26. (Amended) The method according to claim 17, wherein said calibrating probes are [simultaneously] used for positional correction of said bondings.

Please cancel claims 15, 16, and 27-30 without prejudice subject to Applicants' rights to further prosecution of these claims as appropriate.

REMARKS

Claims 1-30 were pending in this application. Pursuant to the Restriction Requirement, adhered to by the Examiner in the pending Action, claims 15, 16, and 27-30 are hereby cancelled without prejudice subject to Applicants' rights to further prosecute these claims as appropriate.

Claims 1-14 and 17-26 are therefore pending.

Claims 1-14 and 17-26 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite on various grounds. Claims 1-14, 17-24, and 26 are rejected under 35 U.S.C. § 102(e) as being anticipated by Garini et al (U.S. Patent No. 5,817,462)("Garini"). Claim 25 is rejected under 35 U.S.C. § 103 as being unpatentable over Garini in view of Kamenstsky et al. (U.S. Patent No. 5,107,422)("Kamentsky").

Claims 1, 3, 4, 10, 11, 12, 14, 17-22, and 26 have been amended to overcome the rejections under § 112. The changes are for purposes of clarity and definition and do not alter the meaning of the claims in light of the specification. No new matter has been added by these amendments.

Specifically, claims 1, 4, 10, 12, 14, 17, 18, and 19 have been amended to correct the spelling of the word "labeled," and claim 19 has been further amended to correct a typographical error in the word "comprises."

Independent claim 1 (and dependent claims 2-14 and 17-26) are rejected under § 112 as indefinite for reciting the word "changes." Applicants submit that the application as filed provides a definite meaning to the word "changes" with respect to biopolymers. The specification describes a method of using labeled detector molecules to bond to biopolymers. The detector molecules are specific to the biopolymers, and bond in a detectable pattern that can be evaluated. In a preferred embodiment, one such labeled biopolymer may be a reference biopolymer such as a normal chromosome. A sample chromosome may also be labeled and compared thereby to the reference. Changes in the sample chromosome, as is described for example in the specification at page 6, line 21, through page 7, line 6 and page 11, lines 9-17, from the reference chromosome may be detected and analyzed. Those of ordinary skill in the art would recognize that "changes" refers to differences such as deletions, additions, substitutions, etc., in the biopolymers in question.

While Applicants submit that the original claim language is definite, claim 1 has been amended to replace "changes in" with "differences between." The method provides a means for determining the differences between a reference and a test or sample biopolymer, and the claim language has been amended to clarify and define the claimed method.

Claim 3 has been held to be indefinite in the phrase "fixedly arranged." The specification makes clear that the biopolymers in question may be sorted, e.g., by gel electrophoresis in a suitable matrix, or otherwise fixed prior to labeling and evaluation. Specification at page 3, lines 10-14. This is distinguished from *in situ* labeling and evaluation of the biopolymers. To clarify this aspect of the invention, claim 3 has been amended to recite that the biopolymers may be immobilzed, a technique well known to the art, on a carrier or in a matrix. This fixing may be with or without, or in the course of, sorting the biopolymers by, e.g., weight or other characteristics.

Claim 11 has been rejected as indefinite for reciting the phrase "stem from." It is submitted that this phrase is a result of translation from the original language, and is intended to mean selected from different libraries. The claim has been amended to so clarify the language.

Claim 20 has been rejected as indefinite for reciting the term "sufficient" with respect to the number of probes. Applicants submit that one of ordinary skill in the art would easily be able to determine how many probes would be "sufficient" for the purposes of the invention. As is set forth in the Action, techniques for evaluating labeled biopolymers by other methods are known. Calibrating probes for other techniques are known, as is the use thereof. Depending on the type of imaging being used, one or more calibrating probes may be necessary to provide accurate adjustments and correlations of readings. The number of probes required for this may vary according to a number of known factors, ranging from the type of polymer being imaged to the equipment used to generate the image. One of ordinary skill in this art would know, or would be able to determine without undue experimentation, how many probes were necessary. Claim 20 has been amended to more clearly recite that the calibrating probes are used to correct, or "normalize" the images for comparison purposes. Because those of ordinary skill in the art, evaluating the images provided by the claimed method, would know or could easily determine the number of probes needed to correct positioning errors or shifts, the claim is not indefinite as amended.

Claim 21 has been rejected as indefinite for reciting the term "interactively" and the phrase "the relative shifts." In the method as explained in part in the specification at page 7, lines 9-19, images of the bonded biopolymers are made using, for example, specific fluorescence filters. The use of such filters may result in a perceived shift in the positions of the individual images. By the claimed method, corrections can be made for these "relative shifts" such that the individual images can be correctly compared. The use of disclosed techniques, such as the use of calibrating probes,

distinguishably labeled. Comparable approaches can be found in Lengauer et al. (Human Molecular Genetics, (1993) 2:505-512)(referring to chromosomal "bar codes").

This type of karyotyping results in a number of color bands corresponding exactly to the number of possible combinations (complete overlap) of the used chromosome fragments each being labeled with one fluorochrome, that is, the image obtained is the binary combination of the particular dyes. Thus, for example, with three different fluorochromes, $3^2 - 1 = 7$ different combinations can be generated; for five fluorochromes, 31 combinations result. See Garini at column 30, lines 30-39.

In the current invention, the evaluation of the biopolymer with detector molecules bonded thereto includes the detection and analysis of a the distinguishable color bands generated, and the plurality of different color ratios resulting from the bonding. See specification at page 5, line 13, through page 6, line 2. Thus, the overlap of two differently labeled chromosome fragments bonded to the biopolymer will yield three distinguishable color bands. By further evaluating the intensity of the bands, the band number can be multiplied by known detection techniques.

Thus, according to the current method, detector molecules are selected, as is known in the art, such that when bonded, the detector molecules will overlap. This mixing of, e.g., chromosome fragments as detector molecules, provides not only the color banding, but, as the biopolymer is scanned in the evaluation, a continuously rising and falling intensity curve. The number of possible different combinations that can be achieved by the enabled ratio analysis is limited only by the noise of the intensity profile. Thus, two partially overlapping fragments can be resolved into a multiplicity of color bands.

Garini specifically uses the described binary analysis, and does not teach or disclose the use of the ratio analysis evaluation. Because this is not disclosed in Garini, Garini cannot anticipate the disclosed invention. To achieve the high banding resolution enabled by the current invention, Garini

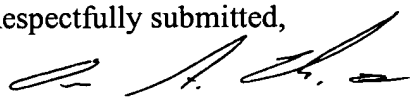
would be required to use a much higher number of differently labeled detector molecules. In comparison to Garini, to achieve comparable results, the current invention makes it possible to greater simplify the complexity of the detector molecule "cocktail" used to bond to the biopolymer. This difference constitutes an element of the current invention that is not disclosed by Garini, and Garini does not anticipate the claimed invention.

Claim 25 is rejected under § 103 as being unpatentably over Garini in view of Kamentsky. For the reasons set forth above, Garini does not provide a teaching of the claimed invention. Kamentsky teaches a method of correcting an image relative to the background thereof, that is, the elimination of light variations in an image. This is not the problem addressed by the calibrating probes of the current invention, which are used to provide color, intensity, and position information for the evaluation of the biopolymers. One of ordinary skill in the art would not consider Kamentsky in solving this problem. Thus, because Garini does not teach the claimed invention, and Kamentsky does not teach the use of a calibrating probe as described, claimed, and used in the current invention, the combination of these references does not render the claim unpatentable.

Applicants submit that the foregoing amendments and remarks demonstrate that the claimed

invention is definite, novel, and unobvious. Applicants request that the rejections be withdrawn, and the claims allowed.

Respectfully submitted,



Oscar A. Towler, III
Registration No. 33,803
Attorney for Applicants
NEXSEN PRUET JACOBS & POLLARD, LLP
P.O. Box 10107
Greenville, SC 29603
Telephone: 864-370-2211
Facsimile: 864-282-1177

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